Remarks

Rejection of the claims for lack of priority The Examiner rejected the claims for lack of priority (see Office Action 9/20/2011 pp. 6-7). More specifically the claims were rejected based on the clauses in claim 91 of *"whereby the length of the segment is greater than or equal to about 47 million base pairs, wherein the subrange of the segment-subrange includes the least common allele frequency 0.1,whereby there are at least about 24 covering markers with least common allele frequencies less than or equal to 0.3 that are distributed within the segment with a density of at least about 1 marker every two million base pairs."*

In response the applicants have amended claim 91 and deleted the two whereby clauses *"whereby the length of the segment is greater than or equal to about 47 million base pairs,"* **and** *"whereby there are at least about 24 covering markers with least common allele frequencies less than or equal to 0.3 that are distributed within the segment with a density of at least about 1 marker every two million base pairs."* The limitation *"wherein the subrange of the segment-subrange includes the least common allele frequency 0.1"* remains in amended claim 91.

As stated previously by the applicants the deleted whereby clauses are not true limitations, see pp. 17-18 of the Amendment/Response of March 10, 2009 which reads: "This whereby clause is not a true limitation *'because a whereby clause that merely states the result of the limitations in the claim adds nothing to the substance of the claim.'* Texas Instruments Inc. v. United States Int'l Trade Comm'n, 988 F.2d 1165, 1172, 26 USPQ2d 1018, 1023-24 (Fed. Cir. 1993); quoted in Lockheed Martin vs. Space Systems/Loral, 249 F.3d 1314. There are other similar 'whereby clauses' in other dependent claims delineating an increased minimum number of covering markers (e.g., about 24, 96, 288 and 1037 markers) with lower least common (minor) allele frequencies; such as minor allele frequencies less than or equal to 0.3, 0.2 or 0.1. …. **Though these whereby clauses are not true limitations, it is the applicants intention that**

these clauses will help to delineate 'the metes and bounds' of the claimed invention(s)."

Since, however, the Examiner has rejected the claims based on these whereby clauses, the applicants have deleted these clauses from the claims. A similar whereby clause in claim 105 has also been deleted. These amendments do not, however, change claim scope.

The Examiner makes no specific individual mention of the remaining limitation in claim 91 (*"wherein the subrange of the segment-subrange includes the least common allele frequency 0.1"*) in the Office Action of 9/20/2010 (page 6). Support for this limitation (including in the priority applications) was previously cited on pp. 55-56 of the Amend/Resp of March 10, 2009. For the Examiner's convenience, the applicants will now repeat the citation of support for this claim limitation in the presently pending claims. In most or all cases the page and line numbers of the relevant sections of these applications will be cited. **For the sake of brevity the following abbreviations will be used:** "'718 app." for the present application 10/037,718, "PCT" for the PCT parent PCT/US99/04376 (filed 26Feb1999), and "Prov. '102" for Provisional priority application 60/076102 (filed 26Feb1998).

Support: A polymorphism with least common allele frequency p = 0.1 has a very prominent role in the description as a sought (or target) disease (or trait-causing) polymorphism that is sought by two-dimensional association based linkage studies described in the application. For example, all of the calculations in Table 2 are based on p = 0.1. See Theory of Operation Sections of '718 app. p. 41, p.42 line 3, PCT p. 40, p. 41 line 3, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10. More specifically in Table 2 the disease allele's frequency is fixed at p=0.1 while the frequency (m) of the positively associated marker allele varies (m = .5, .3, .2, .1, .05) see Theory of Operation Sections of

'718 app. p. 40 lines 10-12, PCT p. 39 lines 1-2, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10.

This description also leads to the description of using lower heterozygosity (lower minor allele frequency, less than or equal to about 0.3, that are "close to 0.1"), markers, rather than just higher heterozygosity markers. See for example '718 app. p. 44 lines 1-2, PCT p. 43 lines 1-2, and Prov. '102 p. 14 lines 14-16.

Thus it is clear that the '718 app., PCT and Prov. '102 describe the least common allele frequency p = 0.1 as a place to look for a trait-causing (e.g., disease) polymorphism on a CL-F map. The present application also describes *"… a rectangular CL-F region, a segment-subrange, that is N covered is used in an association based linkage study to test for the presence of a trait causing bi-allelic gene located within the segment-subrange."* See '718 app. p. 28 lines 5-6, PCT p. 26 lines 34-36, and similar concepts are in Prov. '102 p. 16 lines 49-50, p. 17 lines 4-7, p. 20 lines 2-6. Therefore the present application, (and PCT parent and priority applications) describe a CL-F region that is a segment-subrange that contains the least common allele frequency p = 0.1. (It should be noted the terms "gene" and "trait-causing polymorphism" mean the same thing, see '718 app. p. 1 lines 34-36, PCT p. 1 lines 20-22, and Prov. '102 p. 25 lines 15-19.)
As an example, the Theory of Operation, set/subset example(s) describe covering rectangular CL-F region(s), segment-subrange(s), that include the least common allele frequency p = 0.1; see for example '718 app. pp. 44-47, PCT pp. 43-46, and Prov. '102 p. 75 line 26 to p. 76 line 50, especially lines 36-50.

Finally, the priority rejection of 9/22/2010 (p. 7) cites a lack of *"possession of the claimed set of oligonucleotide compositions (e.g. a disclosure of specific SEQ ID numbers)."* The applicants address the substance of this rejection below in the rebuttal of the Indefiniteness and Written Description Requirement (35 USC 112, 1st and 2nd paragraph) Rejections.

No mention is made in the priority rejection of 9/20/2010 of the limitation in claim 91 of *"wherein the length of the segment of the segment-subrange is greater than or equal to the length of human chromosome 21."* The applicants will, however, now repeat support for this limitation that was previously cited on pp. 54-55 of the Amendment/Response of March 10, 2009. **For support for the limitation** *"wherein the length of the segment of the segment-subrange is greater than or equal to the length of human chromosome 21," t*he application, PCT parent and Provisional priority application describe the segment of a segment-subrange as any length up to the length of an entire chromosome. And individual human chromosomes 1-22, X and Y are described. An example of the chromosomal location coordinates of CL-F points ranging over an entire chromosome, e.g. chromosome number 6, is given. Frequency subranges and chromosomal segments are described. See for example, '718 app. p. 14 lines 2-6, lines 10-13, p. 38 lines 29-30, p. 44 lines 26-27; PCT p. 13 lines 2-6, lines 10-13, p. 37 lines 15-16, p. 43 lines 26-27 and Prov. '102 p. 30 lines 27-30, lines 38-39, p. 40 lines 44-48, and p. 72 lines 37-38.

Each of chromosomes human chromosomes 1-22, and X and Y, including human chromosome 21, is thus an example of a described possible segment (and segment length) of a segment-subrange. The length of each of these example chromosomes is greater than or equal to the length of human chromosome 21, the shortest human chromosome. As stated above, the segment of a segment-subrange is described as any length up to the length of any chromosome. **And the example length of human chromosome 21 then acts as a described "range endpoint" for segment length as in the case In re Wertheim.** See for example, MPEP 2163.05 III. Range Limitations *"In the decision in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of '25%- 60%' and specific examples of '36%' and '50%.' A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at*

least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to 'between 35% and 60%' did meet the description requirement."

Rejection of the claims for indefiniteness The Examiner rejected the claim 91 as being indefinite under 35 USC 112, second paragraph (see pp. 7-9 of the Office Action of 9/20/2010). More specifically the Examiner states (p. 8): *"The claim is directed to a composition. ... A compound cannot comprise method steps. The above limitations appear to be method steps."*

In response the applicants now point out that the claimed invention of claim 91 is directed to a product by process, therefore method limitations in the claim are allowable and appropriate. The Examiner refers (p. 8) to "wherein phrases" such as *"wherein the group of covering markers is chosen so that ….is N covered to within [x, y]"* (see p. 8). These limitations are method limitations or acts (see p. 20 of the RCE, Amend/Resp of 3/22/2010) and are definite to a person of ordinary skill in the art. The choosing of such a group of covering markers is not indefinite to a person of ordinary skill in the art and is clearly described, for example, on p. 10, p. 14 lines 26-32, p. 24 lines 5 to 11. The Examiner also cites the phrase *"wherein the set of oligonucleotides is selected for the set's utility to determine genotype data."* What is generally defined by this limitation are oligonucleotides that are complementary to the markers, see, for example, p. 37 lines 3-16. Selecting complementary oligonucleotides when markers are known is generally a clear and straightforward act for a person of ordinary skill in the art. There is, for example, a generally strong correlation between structure (e.g., complementarity) and function (utility to determine genotype data).

The Examiner also cites unclarity in claims 91, 92, 105 and 212 as to *"what structural limitations of the claimed composition are intended"* pp. 8-9. The applicants now briefly state that the MPEP indicates that structural limitations are not necessary in a product by process claim. Specifically MPEP 2163 II A. 3. (a)

i) (For each claim drawn to a single embodiment or species) reads: *"… disclosure of only a method of making the invention and the function may not be sufficient to support a product claim* ***other than a product-by-process claim****. See, e.g., Fiers v. Revel, 984 F.2d at 1169, 25 USPQ2d at 1605; Amgen, 927 F.2d at 1206, 18 USPQ2d at 1021."* (underlining & emboldening added) The applicants respectfully submit that this is especially true since the applicants request that the claims be examined on the basis that the scope of the claims (for the purposes of infringement, as well as patentability & validity) is limited to products produced by the recited process. The applicants will make further arguments relevant to the Examiner's contention of lack of clarity in claims 91, 92, and 105 below.

Regarding the Examiner's contention of lack of clarity in claim 212 (p. 9), the Examiner states: *"These limitations appear to be intended use limitations and method steps (e.g. generating signals)."* The limitations to which the Examiner refers are, however, (as indicated by a plain reading of the claim) properties of the claimed oligonucleotide composition (product by process). These limitations are not indefinite to a person of ordinary skill in the art. Again, there is generally a strong correlation between the properties recited and structure, once markers are known. A type(1) oligonucleotide is well-defined and definite, see p. 21 lines 18-27 of the present application; and allele-specific oligonucleotides are also definite to a person of ordinary skill in the art. Oligonucleotides with utility as polymerase chain reaction primers are also definite to a person of ordinary skill in the art. An example of the type of signal recited in claim 212 is dye color, see p. 22 lines 10-16. And the labelling of one or more PCR primers by a flourescent dye in order to have utility to generate a dye color is definite. Such labelling is described, for example, in references that are incorporated by reference into the application, such as endnote 10 reference (1) Schuster, et. al. p. 100 *"Forward primers are labelled with either 6-FAM, HEX, or TET flourescent dyes…."* A copy of p. 100 of the Schuster reference has been previously supplied, see Image File Wrapper entry (IFW) dated 7-16-2006 Applicant Arguments/Remarks (REM) for the

present application, last page (page 6). (The journal citation (nature genetics volume 13 1996) and page number (100) are at the bottom of this IFW page copy.) Finally, as is well-known, limitation breadth is not indefiniteness (MPEP 2173.04).

Claim rejections under 35 USC 112, 1st paragraph, the Examiner has rejected claims 91, 92, 105 and 212 for failure to comply with the Written Description Requirement. More specifically the Examiner states that *"one of ordinary skill would have reasonable doubt that the applicant was actually in possession of such oligonucleotide compositions obtained in the way the instant claims describe....."* see p. 10 (bottom) of the 9/20/2010 Office Action.

The top of page 11 of the 9/20/2010 the Office Action of the 35 USC 112, 1st paragraph W. D. Req. Rejection contains a subsection entitled ***Response to Arguments***. The Examiner states in the subsection that *"The applicant's argument filed 3/22/2010 have been fully considered, but are not persuasive.."* That argument (pp. 30-32 of the 3/22/2010 Amend/Response) argued that detailed structure (e.g., specific SEQ ID numbers) were not required to meet the W.D. Req., because the claimed invention is a product by process. The Examiner also states in response to this argument (mid p. 11 of the Office Action of 9/20/2010) that *"In response to applicant's arguments that point to Fiers v. Revel, this case has an entirely different fact pattern from those of the instant claims."*

The applicants respectfully disagree that the relevant facts in Fiers are entirely different. **The subject matter in Fiers, as in the instant claims, deals generally with DNA molecules.** Specifically the single interference count under review in Fiers read: *"A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide."* Significantly this count describes (or defines or claims) a product (DNA), but not a product by process: there are property limitations in the count (i.e., *"codes for a … polypeptide"*), but no process limitations.

In Fiers, as in the instant situation, the enablement of the method of making applicant Fiers's product was not in dispute. The reason applicant Fiers apparently did not prevail despite having an apparently enabled method of making was because the count was directed to a product (not a product by process). As the Court in Fiers noted, *"Fiers has devoted a considerable portion of his briefs to arguing that his method was enabling. The issue here, however, is conception of the DNA of the count, not enablement."*
The Court in Fiers left open the possibility of claiming a product by process in some cases: *"We recognize that, in addition to being claimed by its structure or physical properties, a chemical material can be claimed by means of a process."*
As noted in the MPEP 2163 (Written Description Requirement), specifically 2163 II A. 3. (a) i) *"For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim* ***other than a product-by-process claim.*** *See, e.g., Fiers v. Revel, 984 F.2d at 1169, 25 USPQ2d at 1605; Amgen, 927 F.2d at 1206, 18 USPQ2d at 1021."* (underlining & emboldening added)

Similarly in both Fiers and the instant situation the applicants have argued that the processes of making are straightforward. *"According to Fiers, his method could have been easily carried out by one of ordinary skill in the art."* See also the RCE, Amend/Resp of March 22, 2010, pp. 30-33 (e.g., *"… the process limitations that define each claimed invention are practice-able in a reasonably predictable way"*).

As stated in the MPEP 2163 II A. 3. (a) i) "*Where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied; however, the requirement may not be satisfied where it is not clear that the acts set forth in the specification can be performed, or that the product is produced by that process"*

Given the reasonable predictability and practice-ability of the process limitations that define each claimed invention and the Examiner's withdrawal of the previous enablement rejection of these process limitations, it is reasonable to believe that the claimed process limitations could be performed (at the time of filing of the earliest priority document, Provisional application 60/076,102). And it is also reasonable to believe that the claimed invention (product by process) is produced by the recited process.

In addition, as stated above, there is, for example, a generally strong correlation between structure (e.g., complementarity) and function (utility to determine genotype data). As noted in MPEP 2163 II A. 3. (a) i), *"For example, if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function."* For the reasons stated above, the applicants therefore respectfully submit that a person of ordinary skill in the art would reasonably believe that the applicants had possession of the claimed product by process invention at the time of filing of the earliest priority document (Provisional application 60/076,102).

Another important reason the claimed invention meets the W. D. Req. is that the claimed product by process invention(s) can be distinguished from other materials. This is an important consideration since, as stated in MPEP 2163 I: *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by *"whatever characteristics sufficiently distinguish it"*). And as stated in MPEP 2163 II. A. 2., quoting the Court in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991): *"it is well established in our law that conception of a chemical compound requires that the*

inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it."

This distinguishing of the claimed invention from other materials is made simpler by the fact that the applicants have limited the scope of the claims (for the purposes of infringement) to products made by the recited process or an equivalent process (see p. 71 of the Amend/Resp. of March 10, 2009 and p. 22 of the Supplemental Amend/Resp of June 24, 2010). Given this limiting of the scope of the presently pending claims (for the purposes of infringement) to products made by the recited process or an equivalent process, the applicants respectfully request that the Examiner (and the USPTO) also examine these claims based on the same scope for the purposes of patentability (i.e., validity). That is, the applicants respectfully request that the Examiner (and the USPTO) examine the claims as having the same scope for the purposes of infringement and patentability (i.e., validity). An examination of the claims in this manner makes it especially clear that the claimed invention can be distinguished from other materials. (The applicants also note that the applicants' previous arguments that restriction would not be proper between product by process and process of making claims (Supplemental Amend/Resp of June 24, 2010, pp. 22 & 23) were based in part on such an analysis of claim scope.

The applicants respectfully submit that, given judicial precedent, it is appropriate that the Examiner (and the USPTO) should examine the claims as having the same scope for both the purposes of infringement and validity (patentability). **Some examples of this judicial precedent are as follows:** Amgen Inc. v. Hoechst Marion Roussel, Inc., 324 F.3d 1313, 1330 (Fed. Cir. 2003) (*"It is axiomatic that claims are construed the same way for both invalidity and infringement."*); Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1351 (Fed. Cir. 2001) (*"Because the claims of a patent measure the invention at issue, the claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses."*); C.R. Bard, Inc. v. M3

Systems, Inc., 157 F.3d 1340, 1363 (Fed. Cir. 1998) (*"Claims must be interpreted the same way for determining infringement as was done to sustain their validity."*); Southwall Technologies, Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995) (*"Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers."*); Beachcombers, International, Inc. v. WildeWood Creative Products, Inc., 31 F.3d 1154, 1163 (Fed. Cir. 1994) (*"We have already interpreted the claims for purposes of assessing their validity. The same claim interpretation of course applies to the infringement analysis."*); Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1583 (Fed. Cir. 1991) (*"claims must be construed the same way for validity and for infringement"*); Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 882 (Fed. Cir. 1988) (*"The claims of the '970 patent measure the invention at issue; thus, the claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses."*)

The applicants also note that since March 2009, when the applicants voluntarily limited of the scope of the claims for the purposes of infringement to the recited process or an equivalent, the Courts have similarly limited the scope of product by process claims in Abbott Labs vs. Sandoz, Inc. (CAFC, May 2009).

In addition the applicants respectfully caution the Examiner that contrary to what the Examiner states on p. 10, the limitation *"wherein N is less than maximal, and whereby the number and distribution of known markers in the neighborhood of the CL-F region make it possible for N to be a greater value,"* is no longer present in pending claims 91, 92, 105 and 212.

For all of the above reasons, the applicants respectfully submit that further structural description (e.g., SEQ ID numbers) is not needed for the claimed invention(s) to meet the WD Req. or the definiteness requirement under 35 USC first and second paragraphs. The Examiner is urged to reconsider again the

Arguments on pp. 18-34 (Rebuttal of the Enablement and W.D. Req. Rejections) in the RCE, Amend/Resp of March 22, 2010.

Claim rejection under 35 USC 103 The Examiner has rejected the claims for obviousness under 35 USC 103 (a) in light of references McGinnis, et. al. (WO99/43858, publication date 02 Sept. 1999) and Cohen EP 0 892 068 (publication date 20 January 1999) and Kruglyak, et. al., AJHG, 1995, 57: 439-454, see p. 12 of the Office Action of 9/20/2010.

The applicants respectfully submit that this is not a proper rejection as McGinnis, et. al. and Cohen were both published after the earliest priority date for the earliest priority document (Provisional application 60/076,102, filed 26 Feb 1998). And as noted above under Remarks regarding the Priority Rejection the applicants have argued that the claims (especially in amended form) are entitled to the priority date of 26 Feb 1998. The applicants have made a conscientious effort since at least March 10, 2009 to cite specific support for each claim limitation to ensure support under the W.D. Req. going all the way back to Provisional application 60/076,102, filed 26 Feb 1998. See for example, pp. 51-70 of the Amend/Resp of March 10, 2009 and pp. 23-29 of the Brief Second Supplemental Response and Amendment of June 27, 2010.

For the Examiner's convenience, the applicants will now repeat the citation of support for claim limitations in the presently pending claims. In most or all cases the page and line numbers of the relevant sections of these applications will be cited. **For the sake of brevity the following abbreviations will be used:** "'718 app." for the present application 10/037,718, "PCT" for the PCT parent PCT/US99/04376, and "Prov. '102" for Provisional priority application 60/076102.

Support for the first claim limitation in presently pending (amended) claim 91 was previously cited on pp. 24-25 of the Brief Second Supplemental Response and Amendment of June 27, 2010. That support is now repeated. For support for the limitation *"A composition for use in obtaining genotype data or sample allele frequency data, comprising: one or more copies of a set of*

oligonucleotides, the set of oligonucleotides being complementary to a group of two or more bi-allelic covering markers," see '718 app. p. 37 lines 3-22, PCT p. 35 line 27 to p. 36 line 17 and Prov. '102 p. 64 line 42-52. See also '718 app. p. 34 line 25 to p. 35 line 16, p. 35 line 35 to p. 36 line 27, PCT p. 33 line 20 to p. 34 line 11, p. 34 line 30 to p. 35 line 22, and Prov. '102 p. 60 lines 33-46, p. 52 line 46-53, p. 53 line 12 to p. 54 line 22.

Support for most other claim limitations in claim 91 was previously cited on pp. 52-57 of the Amend./Resp. of March 10, 2009 or p. 26 of the Brief Second Supplemental Response & Amendment of June 27, 2010. That support is now repeated. For support for the limitation *"wherein the set of oligonucleotides is selected for the set's utility to determine genotype data or sample allele frequency data for each of the two or more covering markers"* see '718 app. p. 37 lines 8-22, PCT p. 36 lines 3-17, and Prov. '102 p. 64 lines 42-50. (It should be noted that genotype data for "samples of individuals" that are "groups of individuals who have supplied phenotype data regarding the genetic characteristic and provided chromosomal DNA samples which have been pooled" is sample allele frequency data; see for example Prov. '102 p. 36 lines 23-34.)

For support for the limitation *"wherein the group of covering markers is chosen so that a CL-F region is N-covered to within [x, y] by the covering markers, wherein [x, y] is a two-dimensional distance….N is an integer greater than or equal to 1."* For support see for example, '718 app. p.14 lines 26-28, lines 33-37, PCT p. 13 lines 26-28, lines 33-37, and Prov. '102 p. 30 lines 45-47, lines 52-53, & p. 31 lines 2-4.

For support for the limitation *"wherein x is less than or equal to 1 million base pairs and y is less than or equal to 0.2"* see for example '718 app. p.27 lines 20-23, lines 27-28, 32-33, p. 29 lines 16-17; PCT p. 26 lines 11-14, lines 18-20, p. 28 lines 7-8 and Prov. '102 p. 35 lines 14, 20-22, 44-46, p. 40 lines 18-20.

For support for the claim limitation *"the covering markers and the CL-F region*

being for a species of creatures" '718 app. p. 26 lines 26-27, p. 23 line 17; PCT p. 25 lines 18-19, p. 22 line 8; Prov. '102 in the Definition of a CL-F region *"species under study"* at p. 30 lines 33-34, Title of the Invention: Improved Techniques for Linkage Studies at p. 1 or in the Header at any page, *"in a species of creatures, comprising the steps of: choosing two or more bi-allelic covering markers so that a CL-F region is N covered"* at p. 34 line 11-13.

For support for the claim limitation *"the CL-F region being a collection of one or more points on a two-dimensional CL-F map that is similar to an x-y graph,"* see '718 app. p. 10 lines 26-27, lines 3-4; PCT p. 9 lines 26-27, lines 3-4; Prov. '102 p. 30 line 27, p. 29 lines 1-4.

For support for the claim limitation *"the CL-F map having the two orthogonal dimensions of chromosomal location (CL) and least common allele frequency (F),"* It is well-known that an x-y graph has two orthogonal (i.e., at right angles) dimensions, x and y, see '718 app. p. 10 lines 3-8; PCT p. 9 lines 3-8; Prov. '102 p. 29 lines 1-4. P. 8 lines 8-11. See also Abstract of '718 app. & PCT.

For support for the limitation *"whereby each point in the region is within the distance [x, y] of each of N or more of the covering markers."* This whereby clause is not a true limitation, it follows from the other limitations in the claim and the definition of N-covering. See '718 app. p. 13 lines 34-36 & p. 14 lines 26-28, PCT p. 12 lines 34-36 & p. 13 lines 26-28 and Prov. '102 p. 30 lines 19-21, lines 45-47.

For support for the limitation *"wherein the CL-F region is a segment-subrange."* For support see '718 app. p. 15 lines 19-20, p. 28 lines 4-5; PCT p. 14 lines 19-20, p. 26 lines 34-35 and Prov. '102 p. 27 lines 15-17, p. 40 lines 44-48, p. 72 lines 37-38. The whereby clause "whereby the segment-subrange is a rectangular region on the CL-F map" is not a true limitation. This whereby clause follows from the Description, see '718 app. p. 15 lines 19-20, PCT p. 14 lines 19-20 and Prov. '102 p. 27 lines 15-17. The clause *"whereby the segment-subrange is bounded by a chromosomal segment and a least common allele frequency*

subrange" is not a true limitation, but follows from the definition of segment-subrange; see '718 app. p. 15 lines 17-33, PCT p. 14 lines 17-33, and Prov. '102 p. 27 lines 3-38, and p. 31 lines 5-7.

For support for the limitation *"wherein the length of the segment of the segment-subrange is greater than or equal to the length of human chromosome 21,"* the application, PCT parent and Provisional priority application describe the segment of a segment-subrange as any length up to the length of an entire chromosome. And individual human chromosomes 1-22, X and Y are described. An example of the chromosomal location coordinates of CL-F points ranging over an entire chromosome, e.g. chromosome number 6, is given. Frequency subranges and chromosomal segments are described. See for example, '718 app. p. 14 lines 2-6, lines 10-13, p. 38 lines 29-30, p. 44 lines 26-27; PCT p. 13 lines 2-6, lines 10-13, p. 37 lines 15-16, p. 43 lines 26-27 and Prov. '102 p. 30 lines 27-30, lines 38-39, p. 40 lines 44-48, and p. 72 lines 37-38.

Each of chromosomes human chromosomes 1-22, and X and Y, including human chromosome 21, is thus an example of a described possible segment (and segment length) of a segment-subrange. The length of each of these example chromosomes is greater than or equal to the length of human chromosome 21, the shortest human chromosome. As stated above, the segment of a segment-subrange is described as any length up to the length of any chromosome. **And the example length of human chromosome 21 then acts as a described "range endpoint" for segment length as in the case In re Wertheim.** See for example, MPEP 2163.05 III. Range Limitations "In the decision in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of '25%- 60%' and specific examples of '36%' and '50%.' A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments

outside the "25% to 60%" range, however a limitation to 'between 35% and 60%' did meet the description requirement."

For support for the limitation *"wherein the subrange of the segment-subrange includes the least common allele frequency 0.1,"* A polymorphism with least common allele frequency p = 0.1 has a very prominent role in the description as a sought (or target) disease (or trait-causing) polymorphism that is sought by two-dimensional association based linkage studies described in the application. For example, all of the calculations in Table 2 are based on p = 0.1. See Theory of Operation Sections of '718 app. p. 41, p.42 line 3, PCT p. 40, p. 41 line 3, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10. More specifically in Table 2 the disease allele's frequency is fixed at p=0.1 while the frequency (m) of the positively associated marker allele varies (m = .5, .3, .2, .1, .05) see Theory of Operation Sections of '718 app. p. 40 lines 10-12, PCT p. 39 lines 1-2, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10.

This description also leads to the description of using lower heterozygosity (lower minor allele frequency, less than or equal to about 0.3, that are "close to 0.1"), markers, rather than just higher heterozygosity markers. See for example '718 app. p. 44 lines 1-2, PCT p. 43 lines 1-2, and Prov. '102 p. 14 lines 14-16.

Thus it is clear that the '718 app., PCT and Prov. '102 describe the least common allele frequency p = 0.1 as a place to look for a trait-causing (e.g., disease) polymorphism on a CL-F map. The present application also describes "… a rectangular CL-F region, a segment-subrange, that is N covered is used in an association based linkage study to test for the presence of a trait causing bi-allelic gene located within the segment-subrange." See '718 app. p. 28 lines 5-6, PCT p. 26 lines 34-36, and similar concepts are in Prov. '102 p. 16 lines 49-50, p. 17 lines 4-7, p. 20 lines 2-6. Therefore the present application, (and PCT parent and priority applications) describe a CL-F region that is a segment-subrange that

contains the least common allele frequency p = 0.1. (It should be noted the terms "gene" and "trait-causing polymorphism" mean the same thing, see '718 app. p. 1 lines 34-36, PCT p. 1 lines 20-22, and Prov. '102 p. 25 lines 15-19.)
As an example, the Theory of Operation, set/subset example(s) describe covering rectangular CL-F region(s), segment-subrange(s), that include the least common allele frequency p = 0.1; see for example '718 app. pp. 44-47, PCT pp. 43-46, and Prov. '102 p. 75 line 26 to p. 76 line 50, especially lines 36-50.

Support for limitations in presently pending claim 92 was previously cited on p. 27 of the Brief Second Supplemental Response & Amendment of June 27, 2010 and is repeated here. For support for the limitation *"wherein the CL-F region is for the species of creatures and for a population, wherein the population is a population as in the field of population genetics"* see above for support for *"the CL-F region being for a species of creatures."* For *"for a population"* see for example '718 app. p. 20 lines 8-12, especially line 12, p. 23 line 22, p. 26 lines 26-27 & lines 37-39, PCT p. 19 lines 8-12, especially line 12, p. 22 line 13, p. 25 lines 18-19 & lines 29-31, and Prov. '102 p. 21 lines 45-56, p. 31 lines 20-28, and p. 34 lines 49-56. For *"wherein the population is a population as in the field of population genetics"* (the term population is used in a statistical sense and in the sense the term is used in population genetics), see for example, '718 app. p. 20 lines 23-25, PCT p. 19 lines 23-25; & '718 app. p. 44 lines 21-22, PCT p. 43 lines 21-25, (e.g., *"Finnish population"* and *"more genetically heterogeneous populations"*) and Prov. '102 p. 6 lines 41-42, p. 10 line 29 & 37, p. 21 lines 45-56, p. 31 lines 20-28, p. 36 lines 8-21, especially lines 13-14 (*"population genetics"*) and p. 75 lines 39-42.
For support for the limitation *"wherein each covering marker is an SNP"* see '718 app. p. 35 lines 10-13 & 23, PCT p.34 lines 5-8 & 18, Prov. '102 p. 27 line 51, p. 53 lines 42-43 (e.g., *"thousands of bi-allelic markers"*). For a person of ordinary skill in the art, SNPs would generally be immediately associated with the phrase *"thousands of bi-allelic markers,"* this is explained in more detail on p. 22 of the Amend./Resp. of March 10, 2009 by citing the 1997 Kruglylak reference,

Kruglyak (The use of a genetic map of biallelic markers in linkage studies. Nature Genetics, September 1997, vol.17, pp. 21-24). This Kruglyak references discusses very large numbers of SNPs for use as bi-allelic markers in genetic studies.

Also references incorporated into the applications that support single base or single nucelotide polymorphisms. Specifically the (1) Chee reference recites *"single-base resolution"* in its Abstract and *"single-base polymorphism"* twice (in the mid left column and the bottom of middle column on p. 611). Similarly each of the three (2) Saiki, (3) Wu and (4) Nickerson references recite *"single base"* or *"single nucleotide"* variation in their introductions in the first (leftmost columns) of their first pages. More information on these references follows. See endnote references on p. 125 of Prov. '102 (and endnotes of '718 app. p.50, PCT p. 48):

(1) Accessing Genetic Information with High-Density DNA Arrays, Mark Chee, etal. Science, vol 274, Oct. 25, 1996 , pp. 610 – 614.

(2)Genetic analysis of amplified DNA with immobilized sequence- specific oligonucleotide probes, Saiki,et al. Proc Natl Acad Sci USA vol 86, pp.6230-6234.

(3)Allele-specific enzymatic amplification of β-globin genomic DNA for diagnosis of sickle cell anemia, Wu, et al., Proc Natl Acad Sci USA vol 86 pp 2757-2760.

(4)Automated DNA diagnostics using an Elisa-based oligonucleotide ligation assay, Nickerson, et al., Proc Natl Acad Sci USA vol 87, pp. 8923-8927.

These above four references (and several others) are incorporated by reference into all three applications: '718 app., PCT, & Prov. '102. In addition, reference (1) is listed as reference D1 in the Information Disclosure Statement of 5/19/2008 and a copy of the Chee reference was provided to the Examiner. And each of the (2) Saiki, (3) Wu and (4) Nickerson references is listed in the IDS of June 2009 as one of references AH-AM on sheets 1 and 2.

Support for the limitations in amended claim 105

For support for the limitation *"wherein the subrange of the segment-subrange is the subrange 0 to 01"* this limitation is supported by the fact that the minor allele frequency p = 0.1 plays such an important role in the application(s) as discussed

above. In effect the subrange $p < 0.1$ has been added to $p = 0.1$ to get the subrange $p \leq 0.1$. This is naturally supported and supported by Theory of Operation sections '718 app. p. 43 line 2, p. 45 lines 15-16, PCT p. 42 line 2, p. 44 lines 15-16, and Prov. '102 p. 38 lines 7-8, & p. 82 lines 19-20. These passages describe the possibility of the allele frequency "p" of the sought disease allele D being equal to 0.1 or less than 0.1 (*"below 0.1/above 0.9"*).

For support for the limitation *"wherein N is greater than 2"* Higher values of "N" are preferred, see '718 app. p.27 lines 33-34 and the example of $N \geq 2$ p. 29 lines 17-18, PCT p. 26 lines 24-25, and the example of $N \geq 2$ p. 28 lines 8-9 and Prov. '102 p. 35 lines 46-47, and the examples of $N \geq 2$, p. 11 line 40, p. 41 line 27, and p. 84 line 23. Since higher values of N are preferred and examples of N greater than or equal to 2 are given, then *"N greater than 2"* is supported.

Support for the limitations in claim 212 For support for the limitation *"wherein each oligonucleotide in the set is a type (1) oligonucleotide that is allele-specific,"* see for example, '718 app. p. 35 lines 10-13 and p. 48 lines 4-8; PCT p. 34 lines 5-8, p. 47 lines 4-8 and Prov. '102 p. 53 lines 38-46.

For support for the other limitations in claim 212, see for example, '718 app. p. 22 lines 10-16, especially lines 14-16, p. 35 lines 10-11 and 13-15; PCT p. 21 lines 1-7, especially lines 5-7, p. 34 lines 5-6 and 8-10 and Prov. '102 p. 28 lines 23-28, especially lines 26-28, p. 53 line 39 to p. 54 line 22, especially p. 54 lines 4-22. These passages describe complementary oligonucleotides as PCR primers, signal generation by PCR reactions and a signal such as a dye color.

The Chee reference is also part of these passages. The Abstract of the Chee reference states: *"Sequence polymorphisms were detected with single base resolution…"* The Chee reference is incorporated by reference into '718 app., PCT and Prov. '102. See Remarks above under support for claim 180 for more details regarding the Chee reference.

Given the support cited above that extends back to the earliest priority document (Provisional application 60/076102, filed 26FEB1998) McGinnis, et. al. (WO 99/43858 published 02 Sept 1999) and Cohen (EP0892068

published 20 Jan 1999) cannot properly be used as obviousness references against the currently pending claims.

Conclusion

The applicants have responded to each point of rejection Office Action of 9/20/2010. The applicants have amended claims 91 and 105 to delete “whereby clauses” that the Examiner used as a basis for rejection. And the applicants have submitted extensive Remarks rebutting the rejection of the claims for lack of priority and failure to meet the W.D. Req. and for Indefiniteness. And the applicants have cited extensive support for each pending claim limitation in priority documents to show that an obviousness rejection using later published references is improper. In addition, the applicants have requested that the Examiner & USPTO examine the claims based on having the same scope for the purposes of both infringement and patentability/validity.
For the reasons advanced above, applicants respectfully submit that the claims are now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,

/Robert O. McGinnis/
Robert O. McGinnis
Reg. No. 44, 232
January 20, 2011
1575 West Kagy Blvd.
Bozeman, MT. 59715
tel (406)-522-9355